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Comments of the Biotechnology Industry Organization (BIO) to the Ministry of Health and Social Protection Colombia

12 June 2012

Re: The Partial Amendment to Executive Order 677 of 1995 Which Sets Forth Procedures for Evaluation Applications for the Health Registration of Medicines of Biological Origin

The Biotechnology Industry Organization (BIO) is grateful for this additional opportunity to respond to the *Partial Amendment to Executive Order 677 of 1995 Which Sets Forth Procedures for Evaluation Applications for the Health Registration of Medicines of Biological Origin,* herein referred to as "the Amendment", and we refer you to our previous comments filed on 24 April 2012 for background about BIO and its interest in this Amendment.

At the outset, BIO commends the government of Colombia for its requirement to develop a Centralized Patient Registry and Use of the Drugs of Biologic Origin to track pharmacovigilance among other things. Moreover, BIO commends the government of Colombia for setting forth Health Authority Review timelines which can help facilitate the tracking of the registration process, providing more transparency.

BIO notes that there still does not appear to be a clear distinction between what the Amendment refers to as the "reference medicine" and the "successor medicine" in particular as it relates to demonstrating effectiveness and immunogenicity. Moreover, it is unclear from the Amendment whether the successor medicine must even be a similar molecule to that of the reference molecule. The Amendment sets forth requirements for evaluation of products of biological origin but does not acknowledge the relationship between a reference and successor medicine.

Are these molecules biosimilars of each other, or are they different products of similar function? The use of the terminology "comparability" remains unclear. The term itself implies a comparison between two products. However, this concept is not adequately explained in the Amendment. In this regard, it is important to recognize that similarity and comparability are distinct concepts. For example, in the United States, manufacturers of innovator products are permitted to make post-approval manufacturing changes to their products based upon a showing of comparability between the two products. This is viewed as being appropriate because innovator manufacturers possess a thorough and robust body of knowledge about the process used to manufacture the original product, which can be applied in support of subsequent modifications to the manufacturing process. In contrast, the sponsor of a product of biologic origin which is not the innovator product, but purports to be similar, would not have access to the cell line or the critical manufacturing processes that are essential to production of the innovator product. As a result, new clinical data will be needed to support similarity to an innovator product. Furthermore, it will be necessary to perform a complete analytical comparison with the innovator's product in support of approval of the similar product.

The Amendment makes reference to the possible need for additional requirements, (e.g. comparability, etc.) as the case warrants, it has no requirement for human clinical trials to show comparability and immunogenicity when evaluating a successor medicine. As per BIO's previous response, successor medicines should require a clearly defined regulatory pathway in order to both provide adequate patient safety provisions and enable scientifically justified abbreviation.

BIO once again urges the government of Colombia to continue to ensure that patient safety is not compromised and that incentives for innovation are preserved as it implements its biologics registry scheme. Patients should not have to accept greater risks or uncertainties in using a biological product, whether a successor drug of biological origin or a reference product. Clinical trials appear to be optional in the registration

process for biotechnological products and this can result in unnecessary risks for patients. In BIO's view, clinical comparative trials should be mandatory and not optional.

The Amendment stipulates that there will be mechanisms developed to help interested parties in determining what is necessary for the completion of either comparable or original data. However, the Amendment does not set forth a process. BIO urges that such a process be open and consultative, resulting in the development of clear guidelines for applicants.

In addition to the particular issues concerning scope and terminology, BIO notes that there still appears to be a lack of several topics of importance in the Amendment. These include the recognition of the issues relating to interchangeability or substitution and indication extrapolation. Because of the complex science involved with manufacturing biosimilar medicines, many advanced regulatory agencies[1] have indicated that the generic drug approval pathway is not appropriate for complex biologics. The World Health Organization's guidelines referenced above, may serve as a starting point for any scientifically based regulatory approval pathway for biologics.[2]

In addition, BIO maintains that with respect to Article 6, the criteria as written are not standards or characteristics on which a determination can be made. Therefore, the regulation is discretional and non-obligatory, which is insufficient in terms of requirements for reference medicines and successor medicines. Instead, criteria should be developed that articulates standards or characteristics on which a determination can be made (e.g. approved under an ICH biosimilars pathway). The Amendment also should clarify the accountability of the applicant and INVIMA in accruing the necessary data for evaluation. Moreover, as noted in the general comments, the definition of a drug of "first

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[1] The U.S. Food and Drug Administration, European Medicines Agency, Canadian Health Authority, Australian Medicines Agency, Japan's Ministry of Health, Labor and Welfare have all confirmed that the small molecule regulatory system is inappropriate for biosimilar approval.

[2] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

entry" and other terminology should be clarified so that Article 6 is not read to permit a biosimilar to be considered a Reference product under this section.

The data categories of Article 7 should be included in the required information of Article 5, rather than the "complementary information" category. In addition, as noted above, the language should confirm that comparability is the assessment of the impact of observed differences on safety and efficacy and can include pre-clinical and clinical confirmation. For biosimilars, the need for pre-clinical and clinical data is assumed based on expected product differences resulting from unique cell line, process, purification and container closure systems.

BIO also notes that in Article 9 there is a requirement for the applicant to respond to a decision of the Specialized Office within 60 days. In this regard, it is important to consider the requirements in the decision of the Specialized Office. As an example, if the decision requires additional clinical trials, a full response may be difficult to present within a 60 day time-frame, whereas additional analytical testing may be more easily achievable. In the former case, applicant should be able to provide a plan for addressing the requirements in the decision within the 60 day time frame. BIO urges that in this regard, the applicant be afforded reasonable opportunity to present facts and arguments in support of their positions prior to any final administrative action.

BIO further notes that in Article 11, there is no recourse for an applicant if the result of the evaluation by the Specialized Office is unfavorable. In most regulatory approval regimes, applicant has access to some sort of dispute resolution mechanism or hearing that allows them to air their concerns. BIO recommends that the government of Colombia also consider such a mechanism for drugs of biologic origin. It is instructive to consider the provisions of Article 19.5 of the U.S. Colombia TPA which require the establishment or maintaining of judicial, quasi-judicial, or administrative tribunals or procedures for the purpose of the prompt review and where warranted correction of final administrative actions.

With respect to Article 12, the Amendment should clarify that this Article is not intended for use by biosimilar products and that, in line with the appropriate standards, a product can only become a reference drug through submission of a full registration dossier for each indication.

In Article 17 of the Amendment, BIO notes that there are two different naming schemes for drugs of biologic and biotechnologic origin. This implies that there is a discernible difference between these two types of products. However, there is no reason to believe that such differences exist and that even if they do, they have an impact on the structure and/or function of the biologic product. Moreover, the Amendment should articulate a requirement for distinguishable names for biosimilar products for purposes of accurate prescription by health care professionals, to avoid risks of inappropriate substitution, and for traceability and pharamacovigilance.

Finally, BIO notes that the time frame for existing holders of sanitary registries to comply with the requirements of the present Amendment is shorter than what is considered to be reasonable. Additional requirements for clinical trials, or testing could impact the availability of such products for patients. As often times some of these products are the only ones that are available for use, their absence could create significant access issues for patients.

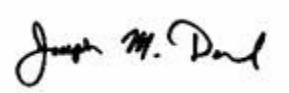
Conclusion

We commend the government of Colombia for taking steps towards developing a sanitary regime for drugs of biological origin. We urge that the regime include a transparent process which ensures patient safety and provides effective protections to incentivize innovation. There should be a transparent statutory and regulatory process which enables manufacturers of first drug of biologic origin to provide full and fair opportunities to engage government authorities and other stakeholders in a meaningful public process. As

such, it is urged that all regulations and guidelines, or proposed amendments to such regulations and guidelines, be publicly available and subject to public notice and comment.

We appreciate the opportunity to express our views. For additional information regarding the positions of The Biotechnology Industry Organization please see http://www.bio.org/category/biosimilars.

Respectfully submitted,



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